REMARKS

Applicants have amended the claims to clarify the location of the extracellular domain, and to clarify the functional limitation previously added to the claims. Claim 51 has been amended to correct a typographical error. Applicants maintain that these amendments add no new matter and are fully supported by the specification as originally filed. For example, support for the amendments can be found in Figure 2 and Example 18 of the specification.

Claims 42-51 remain present for examination. Applicants respond below to the specific rejections raised by the Examiner in the Office Action mailed September 13, 2004. For the reasons set forth below, Applicants respectfully traverse.

Rejection under 35 U.S.C. §101 – Utility

The PTO has maintained the rejection of the pending claims under 35 U.S.C. § 101 as lacking patentable utility. The PTO alleges that the invention lacks either a substantial asserted utility or a well-established utility. Applicants respectfully disagree.

Substantial Utility

The PTO argues that the invention lacks substantial utility because mRNA over-expression does not correlate with protein over-expression. The PTO argues that the references cited by the Examiner in previous Office Actions underscore the unpredictability of the art, such that each case must be considered separately, and there is no data to indicate that the protein of SEQ ID NO:2 or that which is at least 95% identical to SEQ ID NO:2 is over-expressed in tumor. Further, the PTO notes that the claims are directed to the polypeptide, and therefore utility lies in the utility of the polypeptide. Applicants respectfully traverse.

Utility need NOT be Proved to an Absolute Certainty – a Correlation between the Evidence and the Asserted Utility is Sufficient

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of

> statistical certainty. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not. M.P.E.P. at § 2107.02, part VII (2004) (emphasis in original, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured increase in gene expression in cancer cells establishes a "significant probability" that the encoded polypeptide will also be overexpressed in cancer based on "a reasonable correlation therebetween".

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the PRO180 polypeptide is useful as a diagnostic tool for cancer.

Applicants have established that the Gene Encoding the PRO180 Polypeptide is Differentially Expressed in Certain Tumors compared to Normal Tissue such that the Polypeptide is Useful as a Diagnostic Tool

Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the gene encoding the PRO180 polypeptide, as well as the PRO180 polypeptide. The differential expression of the nucleic acid encoding PRO180 can be used to distinguish cancerous tissue from normal tissue.

In the present Office Action, the PTO has not offered any reason to reject the Grimaldi or Polakis declarations previously submitted. Applicants remind the PTO that the applicant need **not** provide evidence such that it establishes an asserted utility "as a matter of statistical certainty." M.P.E.P. at § 2107.02, part VII (2004). Applicants therefore submit that they have established that the gene expression data reported in Example 18 are significant, and the utility for the PRO180 DNA in distinguishing between normal and cancerous tissue has been established. For the reasons discussed below, this leads to utility for the PRO180 polypeptides as well.

Applicants have established that the Accepted Understanding in the Art is that there is a Reasonable Correlation between Gene Expression and Expression of the Encoded Protein

Applicants next address the PTO's argument that the invention lacks utility because the overexpression of the nucleic acid is not relevant to the utility of the protein, and there is no evidence that the protein is overexpressed. The PTO cites Chen *et al.* (Molecular and Cellular Proteomics 1:304-313, 2002) for the proposition that there is no *necessary* correlation between gene over-expression and protein over-expression. The PTO also cites Genes VI, Benjamin Lewin, 1997, Chapter 29- Regulation of Transcription, to support its position that there is no *inevitable* correlation between mRNA levels and protein levels. The PTO concludes that because there is no *necessary* correlation between gene expression and protein expression, the art is unpredictable and therefore data is required to prove that the protein of SEQ ID NO:2 or that which is at least 95% identical to SEQ ID NO:2 is overexpressed in tumor.

As discussed above, evidence of utility does not have to be to an absolute certainty, and therefore there does not need to be a *necessary* connection between gene expression and protein expression. Rather, there need only be a *reasonable* correlation between the evidence offered

and the asserted utility such that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.

Applicants have previously submitted a copy of a Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be overexpressed." Similarly, the previously submitted declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology states that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." Polakis Declaration, paragraph 6. He cites as supporting evidence not only his years of personal experience, but also results from experiments related to the present application. He reports that for the mRNAs overexpressed in cancer that have been examined, 80% had correspondingly higher levels of the encoded protein. Polakis Declaration at paragraphs 4 and 5.

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (4th ed. 2002) submitted herewith as Exhibit 1). Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA.*" Id. at 302, emphasis added. Similarly, figure 6-90 on page 364 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Id. at 364. This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Id. at 379.

Additional support is found in Zhigang et al., World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 2. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" (see page 6 of Exhibit 2). Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The

authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human Pca, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 2, page 11. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Id. This reference provides additional support for Applicants' position that there does not need to be a *necessary* connection between gene expression and protein expression. Rather, there need only be a *reasonable* correlation between the evidence offered and the asserted utility such that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.

Together, the declarations of Grimaldi and Polakis, the accompanying references, the excerpts from "Molecular Biology of the Cell" and Zhigang et al. all establish that the accepted understanding in the art is that there is a *reasonable* correlation between gene expression and the level of the encoded protein. Evidence of utility does not have to be to an absolute certainty; Applicants have demonstrated the differential expression of the gene encoding PRO180 and have provided sufficient evidence to show that there is a reasonable correlation between expression of the gene and the level of PRO180 protein.

In arguing against this assertion, the PTO cites two references. The PTO relies on Chen et al. (Molecular and Cellular Proteomics 1:304-313, 2002) for the proposition that protein expression does not correlate with gene over-expression and thus the art is unpredictable. Chen et al. found that 21.4% (21 of 98 genes) from lung tissue showed a statistically significant correlation between protein and mRNA expression. It is true that there is no *necessary* correlation between gene expression and protein expression because there are other mechanism for regulating gene expression. However, while the article states that "[t]he use of mRNA expression patterns by themselves...is insufficient for understanding the expression of protein products" it goes on to say that "[b]y combining proteomic and transcriptional analysis of the same samples, however, it may be possible to understand the complex mechanisms influencing protein expression in human cancer." Thus, this article recognizes the role of both mRNA and protein in the diagnosis and evaluation of cancer.

The citation from Genes VI relied upon by the PTO offers even less support for the PTO's position. The PTO relies on the statement that "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." (Genes VI, Benjamin Lewin, 1997, Chapter 29 – Regulation of Transcription, 1st page). The PTO focuses on the statement that "production of RNA cannot inevitably be equated with production of protein." What the PTO ignores is the statement that "it is clear that the **overwhelming majority** of regulatory events occur at the initiation of transcription." This same reference states that transcription of a gene "is a major control point: probably **it is the most common level of regulation**." Id., emphasis added. This reference provides additional support for Applicants' position that that the accepted understanding in the art is that there is a *reasonable* correlation between gene expression and the level of the encoded protein.

Further, Meric, et al., Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 3, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric et al. at 971 (emphasis added).

This statement also supports Applicants' asserted utility. It is true that there is no *necessary* correlation between gene expression and protein expression because there are other mechanism for regulating gene expression. However, were there no significant correlation between gene expression and protein levels, exploiting differences in gene expression between cancer cells and normal cells would not be a "fundamental principle of molecular therapeutics in cancer."

In light of the lack of significant support for the PTO's argument, Applicants submit that the PTO has failed to establish a reason for one of skill in the art to doubt the asserted utility. Even if it has, Applicants have offered sufficient evidence to rebut the PTO's argument and establish that there is a reasonable correlation between gene expression and protein expression. The PTO is again reminded that absolute predictability is not required. Applicants have established that it is more likely than not that one of skill in the art would be convinced, to a

reasonable probability, that the PRO180 protein is differentially in certain cancers as compared to normal tissue, and therefore has utility as a diagnostic tool.

Conclusion

Given the totality of the evidence provided, Applicants submit that they have established a credible, substantial, and specific utility for the claimed polypeptides as diagnostic tools. According to the M.P.E.P. and case law cited above, irrefutable proof of a claimed utility is **not** required. Rather, a specific and substantial credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants have offered sufficient evidence to establish that there is a reasonable correlation between gene expression and protein expression. Applicants have established that it is more likely than not that one of skill in the art would be convinced, to a reasonable probability, that based on the gene expression data for the gene encoding PRO180, the PRO180 protein is differentially expressed in certain cancers, and therefore has utility as a diagnostic tool. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112 – Enablement

The PTO has maintained its rejection of Claims 42-51 under 35 U.S.C. § 112, first paragraph. The PTO states that since the claimed invention is not supported by either a specific asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Applicants believe that the evidence, declarations, references, and arguments discussed above make clear that Applicants have established that it is more likely than not that one of skill in the art would be convinced, to a reasonable probability, that the PRO180 protein is overexpressed in rectal tumors as compared to normal rectal tissue, and in normal lung as compared to lung tumors, and therefore has utility as a diagnostic tool for detecting lung and rectal tumors. This would include the use of the claimed polypeptides to create diagnostic and therapeutic antibodies. This use is disclosed in the application, and the techniques for the creation of antibodies are well known and routine in the art. Thus, at least one use of PRO180 polypeptides is adequately enabled, which is all that is required – "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." M.P.E.P. 2164.01(c). In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112 – Written Description

The PTO has maintained its rejection of Claims 42-43 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The PTO states that "only SEQ ID NO:1 is amplified in tumors which encodes SEQ ID NO:2 and there is no polypeptide that is overexpressed in rectal tumors. Describing assays to find the polypeptide does not describe such polypeptides. The specification does not describe any other nucleic acid that encodes any polypeptide that is 95-99% identical to SEQ ID NO:2 which is encoded by a nucleic acid that is over-expressed in rectal tumors."

The rejection of Claims 42-43 and 50-51 for lacking written description is also maintained. According to the PTO, the specification does not describe how to make polypeptides that are 95-99% identical to SEQ ID NO:2, wherein the nucleic acid is overexpressed. "One would not know how to make or use such molecules."

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of

his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. It is well established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The subject matter of the rejected claims concerns polypeptides having a sequence identity of 95-99% with the specified polypeptide sequence of SEQ ID NO: 2, and as amended, with the functional recitation: "wherein said isolated polypeptide is more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively." Based on the detailed description of the cloning and expression of variants of PRO180 in the specification, the description of the gene expression assay, the actual reduction to practice of SEQ ID NOs:1 and 2, and the functional recitation in the instant claims, Applicants submit that one of skill in the art would know that Applicants possessed the subject matter of the pending claims. Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §102(a)

The Examiner has rejected Claims 42-45, 47 and 50-51 under 35 U.S.C. §102(a) as anticipated by Feng et al. The Examiner states that "applicants may file a 131 declaration to overcome the reference with a 5/99 date." Applicants submit herewith the declaration, and request that the rejection be withdrawn.

CONCLUSION

In view of the above, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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